T2

with E2A-PBX1 translocation in pre B leukaemias and in childhood acute leukaemias [human papilloma virus proteins, Epstein-Barr virus proteins, HTLV-1 proteins, hepatitis B virus proteins, hepatitis C virus proteins, herpes-like virus proteins and HIV encoded proteins].

Remarks

Claims 1-3, 5-18, and 27 are pending. Claims 1 and 27 have been amended. Claims 5 and 9-13 have been canceled. Claims 9-13 and 27 have been withdrawn from consideration as being drawn to a non-elected invention.

With regard to amended claim 1, the applicant respectfully requests that the Examiner note that the specification gives examples of killing cells using CTLs according to claim 1 for several tumor-associated self-antigens: mdm-2 and cyclin D1. There is extensive experimental data presented in the specification. In particular, Example 1, pages 41 to 52, there is a description of the use of CTLs to kill cells that express the tumor-associated antigen mdm-2 (for example, see page 47, section headed "Allo-restricted CTL lyse tumor cells but not normal cells"). Also, Example 3 on page 57, and in particular Figure 7 referred to therein, shows that it is possible to make cyclin D1-peptide-specific, allo-restricted CTL displaying tumor cell killing properties.

The applicant is enclosing two references (Bellantuono *et al.*, 2002; and Gao *et al.*, 2000) which clearly illustrate that the invention can be applied when the antigen is Wilm's tumor antigen, WT1, a self-antigen associated with leukemia (please see, in particular, the paragraph spanning columns 1 and 2 on page 2202 of Gao *et al.*, and the Abstract of Bellantuono *et al.* which indicates that the allo-restricted approach of the claimed invention can produce CTL

which can kill CD34+ progenitor cells form HLA-A2+ leukemia patients, but not from HLA-A2+ healthy individuals).

The present invention is directed to treating cancers where there is an overexpression of a self antigen such as mdm-2 and cyclin D1. The particular CTL's defined in the pending claims (i.e. those wherein the HLA class I complex (or equivalent) type presenting the peptide in the cells to be killed is not present in the CTLs to be administered) are found to be effective in this situation. The Examiner will appreciate that it is generally very difficult to get the immune system to recognize a "self" protein as foreign and kill cells which express the "self" protein.

Rejection Under 35 U.S.C. § 112, first paragraph

Claims 1-3, 5-8, and 14-18 were rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor had possession of the claimed invention. Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

The Examiner has asserted that the specification does not provide written support for "abnormal antigens" nor any "mutant polypeptides". Soley to facilitate prosecution, applicant has remove the objected to terms. This should not be construed as an admission that applicants agree with the examiner's characterization of the term.

Rejection Under 35 U.S.C. § 112, second paragraph

Claims 1-3, 5-8, and 14-18 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

The Examiner asserts that neither the specification nor the claims adequately delineate the metes and bounds of the claimed invention, in particular regard to the terms, "abnormal antigen" or "mutant polypeptide". In response, the applicant has removed the terms asserted to be indefinite.

Rejection Under 35 U.S.C. § 102

Claims 1-3, 5-8, and 14-18 were rejected under 35 U.S.C. § 102(b) as being anticipated by *Journal of Immunotherapy*, 14, 305-309 by Falkenburg *et al.* ("Falkenburg"). Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

Falkenburg

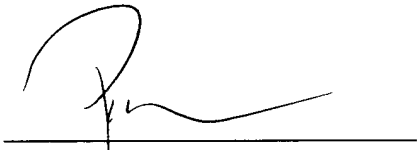
The applicant respectfully submit that the examiner has misinterpreted Falkenburg. The CTL of Falkenburg are derived from allogeneic, HLA-identical donors. This nomenclature refers to CTL that are allogeneic with respect to minor histocompatibility antigens, but not with respect to HLA antigens. Thus, Falkenburg describes "classical" HLA-restricted CTL. They are not allo-HLA-restricted, which is the essence of the presently defined invention. It is critical that the Examiner understand that the CTLs, which kill the cell, *do not contain the HLA molecule which displays the antigen in the cell to be killed.* This is the "allo-HLA-restriction" referred to in the present specification. The fact that the CTL are not allo-HLA-restricted in Falkenburg, is

clearly stated in the first sentence of the Discussion: "...and the T lymphocytes from the ***HLA-genotypically identical*** sibling donors as responder cells..." (emphasis added).

In view of the foregoing discussion, the applicant respectfully submits that Falkenburg does not contemplate the invention as defined by the claims as pending.

Allowance of claims 1-3, 5-18 and 27 is respectfully solicited.

Respectfully submitted,



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Date: February 5, 2003

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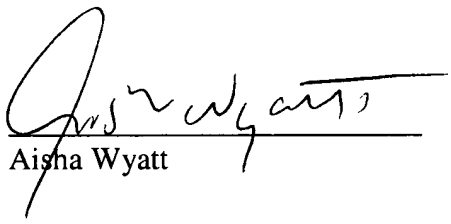
Certificate of Mailing Under 37 C.F.R. § 1.8(a)

I hereby certify that this paper, along with any paper referred to as being attached or enclosed, is being deposited with the United States Postal Service on the date shown below with sufficient postage as first-class mail in an envelope addressed to the Commissioner for Patents, Washington, D.C. 20231.



Aisha Wyatt

Date: February 5, 2003

Marked Up Version of Amended Claims

Pursuant to 37 C.F.R. § 1.121(c)(1)(ii)

1. (Six times amended) A method of killing cells in a patient, the method comprising,

administering to the patient a therapeutically effective amount of cytotoxic T lymphocytes (CTL),

wherein the CTLs have a different HLA class I complex (or equivalent) than the cells to be killed, and

the CTLs specifically recognize a peptide portion on the cells to be killed of [(a) an abnormal antigen or (b)] an antigen which is abnormally elevated in the patient [or (c) an infectious agent protein antigen], when the peptide is presented by the HLA class I complex (or equivalent) on the surface of cells to be killed, wherein the HLA class I complex (or equivalent) type presenting the peptide in the cells to be killed is not present in the CTLs to be administered to the patient, and

the CTLs kill the presenting cells.

2. A method according to Claim 1 wherein the CTL are a clonal population of CTL.

3. (Amended) A method according to Claim 1 wherein the CTL are substantially free of other cell types.

Please cancel claim 5.

6. (Three amended) A method according to Claim 1 wherein the antigen is present at an abnormally elevated amount in the cells to be killed compared to other cells.

7. (Twice Amended) A method according to Claim 1 wherein the cells to be killed are cancer cells.

8. A method according to Claim 7 wherein the cancer is any one of breast cancer; bladder cancer; lung cancer; prostrate cancer; thyroid cancer; leukaemias and lymphomas such as CML, ALL, AML, PML; colon cancer; glioma; seminoma; liver cancer; pancreatic cancer; bladder cancer; renal cancer; cervical cancer; testicular cancer; head and neck cancer; ovarian cancer; neuroblastoma and melanoma.

Please cancel claims 9-13.

14. (Amended) A method according to Claim 1 further comprising the step of determining the HLA class I (or equivalent) molecule type of the patient prior to administration of the CTL.

15. (Amended) A method according to Claim 14 wherein the type is determined using DNA typing.

16. (Amended) A method according to Claim 1 wherein the patient is human.

17. (Twice Amended) A method according to Claim 14 wherein the cytotoxic T lymphocyte is selected from a library of CTL clones, the library comprising a plurality of CTL clones derived from individuals with differing HLA class I (or equivalent) molecule type and each CTL clone recognises the cells to be killed.

18. (Twice Amended) A method according to Claim 17 wherein each CTL clone recognizes at least part of the same molecule contained in or associated with the cells to be killed.

27. (Four times amended) A method according to claim 1 wherein the antigen is selected from the group consisting of cyclin D1, cyclin E, mdm 2, EGF-R, erb-B2, erb-B3, FGF-R, insulin-like growth factor receptor, Met, myc, a p53, BCL-2, a polypeptide associated with the BCR/ABL translocation in CML and ALL, a CSF-1 receptor, an APC, a RET, an EGFR, a polypeptide associated with PML/RARA translocation in PML, and a polypeptide associated with E2A-PBX1 translocation in pre B leukaemias and in childhood acute leukaemias [human papilloma virus proteins, Epstein-Barr virus proteins, HTLV-1 proteins, hepatitis B virus proteins, hepatitis C virus proteins, herpes-like virus proteins and HIV encoded proteins].